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(54) **Anellated indole derivatives.**

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EP 0 297 651 B1

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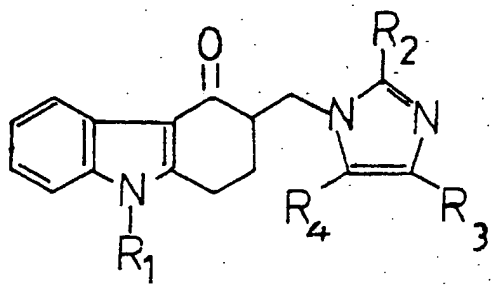
Description

The invention relates to a group of new anellated indole derivatives which are substituted with an imidazolylmethyl group, to the preparation thereof, and to compositions which comprise at least one of these compounds as an active substance.

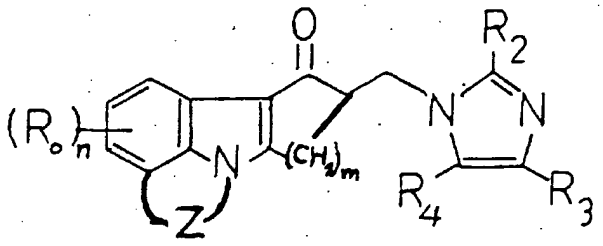
It is known from Belgian Patent Specification No. 901576 and European Patent Application No. 86305671.9 (publication no. 0210840) that carbazolone compounds of formula 1



(1)

wherein R_1 is hydrogen, alkyl having 1-10 C-atoms, cycloalkyl having 3-7 C-atoms, alkenyl having 3-6 C-atoms, phenyl or phenylalkyl (1-3 C in the alkyl group), or a group CO_2R_5, COR_5, $CONR_5R_6$ or SO_2R_5, respectively (wherein R_5 and R_6 may inter alia be alkyl or cycloalkyl), and wherein one of the groups R_2, R_3 and R_4 is hydrogen, alkyl (1-6 C), cycloalkyl (3-7 C), alkenyl (2-6 C) or phenylalkyl (1-3 C in the alkyl group), and the two other groups may be hydrogen or alkyl (1-6 C), are strong and selective antagonists of "neuronal" 5-hydroxytryptamine (5-HT) receptors.

It has surprisingly been found that compounds of formula 2



(2)

wherein

- R_o is alkyl or alkoxy having 1-4 C-atoms, phenylalkoxy having 1-3 C-atoms in the alkoxy group, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, or a group $R_7S(O)_p$, wherein R_7 is alkyl having 1-4 C-atoms and p has the value 0, 1, or 2, or R_o is a group R_8R_9N, R_8R_9N-CO-CH_2- or R_8R_9-N-CO wherein R_8 and R_9 are hydrogen or alkyl having 1-4 C-atoms or R_8R_9N forms a saturated 5- or 6-ring and n has the value 0, 1 or 2, Z together with the carbon atom and nitrogen atom to which Z is bound and the intermediate carbon atom, forms a heterocyclic group consisting of 5-8 ring atoms, in which, in addition to the nitrogen atom already present, a -CO-group or a second hetero atom from the group N, O, S, S-O or SO_2 may be present, which ring may be substituted with 1-3 alkyl groups having 1-4 C-atoms, a phenyl group or a spiroalkyl group (C_2-C_5), or which ring may be anellated with a saturated or non-saturated carbocyclic or heterocyclic ring which consists of 5- or 6-ring atoms and which may be substituted with halogen, alkyl or alkoxy having 1-4 C-atoms, and

m has the values 1-5,

- one of the groups R_2, R_3 and R_4 is hydrogen, alkyl having 1-6 C-atoms, cycloalkyl having 3-7 C-atoms, alkenyl having 2-6 C-atoms or phenylalkyl having 1-3 C-atoms in the alkyl group, and the two other groups independently of each other are hydrogen or alkyl having 1-6 C-atoms, and the pharmaceutically acceptable acid addition salts thereof have a similar but considerably longer-lasting effect and a lower toxicity than the known compounds of formula 1.

Suitable acids with which the compounds of formula 2 according to the invention can form pharmaceutically acceptable acid addition salts are, for example, hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids, for example, citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluenesulphonic acid, methanesulphonic acid, and the like.

The carbon atom to which the imidazolylmethyl group is bound is a centre of chirality. Also chirality can occur when the rings are substituted. Both the racemates and the individual enantiomers of compounds of formula 2 belong to the invention.

The antagonistic activity of the compounds of formula 2 on the response induced by 5-HT or 2-methyl-5-HT was determined and measured in the Bezold-Jarish reflex test in rats. The compounds appeared to have a good antagonistic activity in this test when administered in an intravenous dose of less than 100µg/kg.

The affinity for "neuronal" 5-HT receptors has also been determined and measured by means of the displacement of (^{3}H) GR 38032 F in neuroblastoma cells. In this test pK_i-values of more than 7.0 have been found.

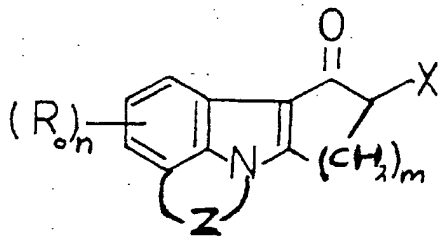
On the basis of the antagonistic activity on this type of 5-HT receptors, the compounds may be used for the treatment of symptoms which are caused by over-stimulation of the said receptors a) in the gastrointestinal system (nausea and vomitting as a result of exogenic factors, for example, cancer therapy, or endogenic factors, for example, stasis of the stomach and migraine), ulcer, dyspepsia, etc., or b) in the central nervous system (hallucinations, delusions, manias, anxiety, pain, vigilance improving, etc.), or c) in the cardio-vascular system, for example, spasms of the vessels, arrhythmias, etc., or d) in the respiratory system (including nasal disorders and disorders in the bronchi and lungs.

The compounds according to the invention and their salts can be brought into forms suitable for administration, for example, pills, tablets, coated tablets, capsules, powders, injection liquids and the like by means of methods conventionally used for this purpose and while using suitable auxiliary agents, for example, solid or liquid carrier materials.

The dosage in which the compounds according to the invention may be used depend on the severity and the nature of the disease to be treated and on the way of administration. As a rule, the dosage will be between 0.05 and 20 mg, preferably between 0.1 and 10 mg of active substance daily.

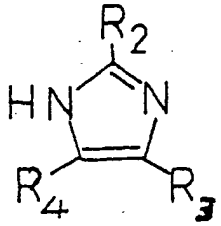
The compounds according to the invention may be prepared in a manner known for analogous compounds. Suitable methods of preparing this type of compounds are described, for example, in the above-mentioned European Patent Application published under number 0210840.

In particular the compounds of formula 2 can be obtained in a good yield by reaction of a compound of formula 3



(3)

wherein R_0, n, m and Z have the above meanings, and X is a reactive group, preferably the group $=CH_2$ or $-CH_2N(CH_3)_2$, with an imidazole compound of formula 4

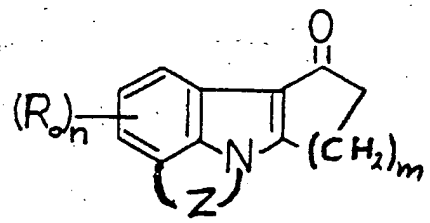


(4)

or a salt thereof, wherein R_2, R_3 and R_4 have the above-mentioned meanings.

The reaction is preferably carried out in a suitable solvent, for example, water, alcohol, dimethylformamide, etc. at temperatures between 20 °C and 150 °C.

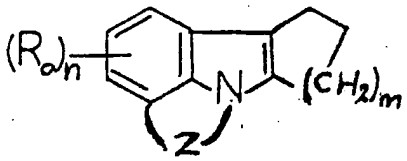
The starting compounds of formula 3 to be used in this reaction can be obtained, for example, by reaction of a compound of formula 5



(5)

wherein R_o, n, m and Z have the above-mentioned meanings, with formaldehyde and dimethylamine hydrochloride, preferably in an organic solvent, for example, acetic acid or alcohol, while heating.

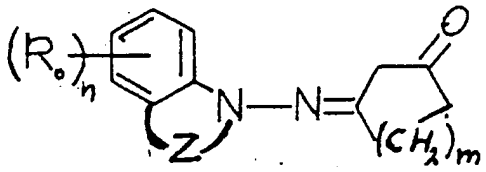
The starting substances of formula 5 can be prepared in a manner known for analogous compounds by oxidation of a compound of formula 6



(6)

wherein R_o, n, m, and Z have the above meanings, with a suitable oxidation agent, for example, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or selenium dioxide preferably in a suitable solvent, for example, water, tetrahydrofuran or dioxan. In particular the starting substances of formula 5 can be obtained in a good yield by oxidation with DDQ of the analogous compounds of formula 6 in tetrahydrofuran and water at tempeatures between -10 and 20 °C as described for similar compounds in J. Org Chem. 42, (1977), p 1213. The compounds of formula 6 are known compounds or can be obtained analogously to known compounds.

Further the starting substances of formula 5 can be obtained in a manner known per se by ring closure of compounds of formula 7



(7)

wherein R_o, n, m and Z have the above-mentioned meanings. This ring closure reaction may be carried out, for example, by boiling in an organic solvent, for example, acetic acid in the presence of an acid catalyst, for example, concentrated hydrochloric acid or sulphuric acid.

The compounds of formula 7 are known compounds or can be obtained analogously to known compounds.

The invention will now be described in greater detail, by way of example, with reference to the ensuing specific examples.

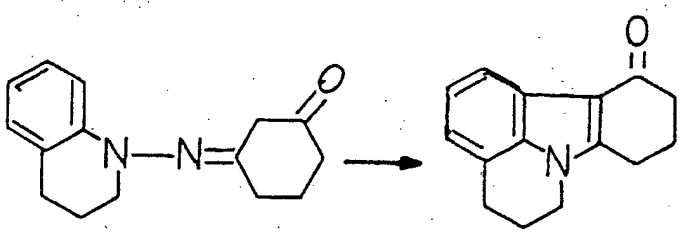
EXAMPLE I

4,5,6,8,9,10-hexahydro-10-[2-methyl-1H-imidazol-1-yl)methyl]-11H-pyrido-[3,2,1-jk] carbazol-11-one

a) Preparation of a compound of formula 7.

A mixture of 46.3 g (313 mmol) of 1-amino-1,2,3,4-tetrahydroquinoline and 38 g (329 mmol) of cyclohexanedione-1,3 in 150 ml of absolute ethanol was boiled for 1 hour while stirring. The reaction mixture was then evaporated to dryness and the residue was dissolved in 100 ml of methanol. 200 ml Of ethyl acetate were added to the resulting solution, after which the mixture was left to crystallize. After leaving to stand overnight at 0 °C and sucking off, 48.3 g of pure product were obtained. Another 19,8 g of product were recovered from the mother liquor. Overall yield 68.1 (90%) having a melting-point of 153-156 °C.

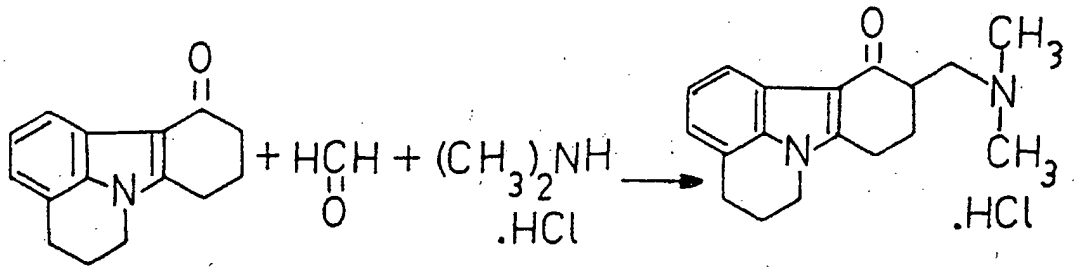
b) Preparation of a compound 5 by ring closure of a compound 7.



(7') (5')

66.1 g of the hydrazone 7' obtained in a) were mixed with 600 ml of acetic acid and 100 ml of concentrated hydrochloric acid. This mixture was boiled while stirring under an atmosphere of nitrogen for 1 hour. After leaviing to stand overnight the mixture began to crystallize. After leaving to stand one day at room temperature and overnight at 0 °C, sucking off, washing with ethanol and water, and drying, 23.5 g of product were obtained (melting-point 173-174 °C). Another 13.1 g of pure product were obtained from the mother liquor after chromatography. Overall yield 36.6 (60%).

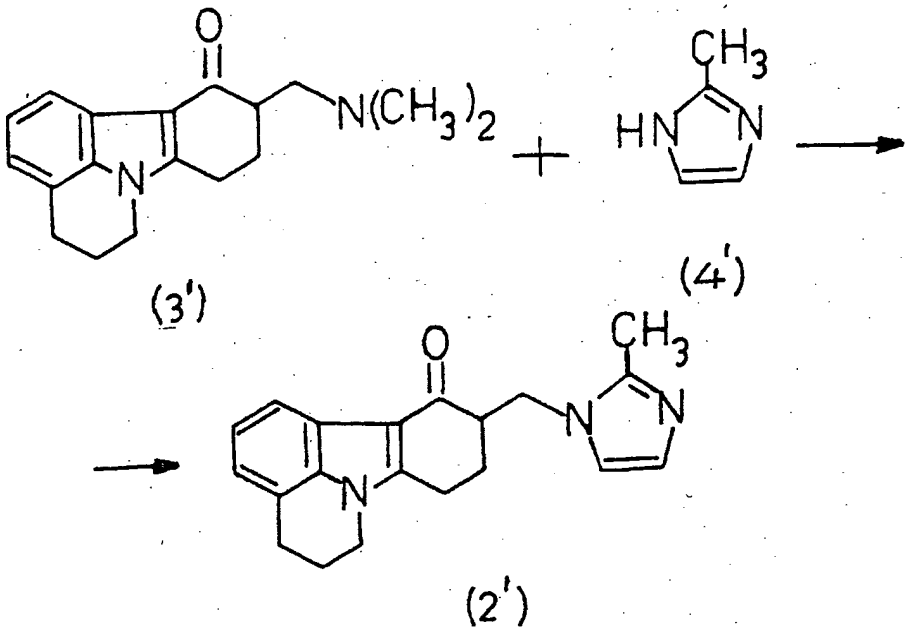
c) Preparation of compound 3 from compound 5



(5') (3')

6.75 (30 mmol) of the ketone of formula 5' were mixed with 1.8 g (60 mmol) of paraformaldehyde, 5.4 g (66 mmol) of dimethylamine hydrochloride and 90 ml of acetic acid, and the mixture was heated in a bath of 100 °C for 3 hours. After evaporating to dryness the residue was rendered alkaline with 2N NaOH and taken up in water, shaken with dichloromethane, evaporated to dryness and chromatographed. After evaporating the good fraction 5.1 g of the free base of compound 3' were obtained. This base was dissolved in 25 ml of boiling ethanol to which 2 ml of concentrated hydrochloric acid were added. The crystallised hydrochloride 3', after leaving to stand overnight at 0 °C, was sucked off, washed with ethanol and dried, 5.1 g (53%) of product being obtained (melting-point) 208-209 °C).

d) Reaction of a compound 3 with a compound 4



3.2 g (10 mmol) Of the salt 3' obtained according to c) were mixed with 2.5 g (30 mmol) of 2-methylimidazole and 30 ml of water. The mixture was boiled for 20 hours under nitrogen while stirring. After cooling, while stirring, the product crystallised. After cooling to 0 °C, sucking off, drying and chromatographing, 2.8 g (87%) of the desired compound of formula 2' were obtained (melting-point 183-184 °C).

EXAMPLE II

a) 4H, 8H-5,6,9,10,11,12-hexahydro-cyclohepta-[4,5]-pyrrolo[3,2,1-ij]-quinoline-12-one

A solution of 25 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (110 mmol) in 250 ml of tetrahydrofuran is added dropwise in 1.5 hours while stirring and at -5 - 0 °C to a solution of 12.2 g of 4H, 8H-5,6,9,10,11,12-hexahydrocyclohepta-[4,5]-pyrrolo-[3,2,1-ij-quinoline (54 mmol) in 500 ml of tetrahydrofuran and 50 ml of water. After everything has been added dropwise, stirring is continued for another 2-3 hours at 0 °C. Approximately 200 ml of silicagel are then added and the whole is evaporated to dryness. After chromatographing twice and after evaporating the good fraction. 2.7 g of product (21%) are obtained (melting-point 141-143 °C).

b) 4H,8H-5,6,9,10,11,12-hexahydro-11-[(dimethylamino) methyl]-cyclohepta-[4,5]-pyrrolo-[3,2,1-ij]-quinolin-12-one.hydrochloride

2.7 g (11.3 mmol) of 4H,8H-5,6,9,10,11,12-hexahydrocyclohepta-[4,5]-pyrrolo-[3,2,1-ij]-quinolin-12-one are mixed with 0.68 g (22.6 mmol) of paraformaldehyde, 2.0 g (25 mmol) of dimethylamine hydrochloride and 50 ml of acetic acid, and the mixture is heated in a bath of 100 °C for 1 hour. After evaporating to dryness the residue is rendered alkaline with 2N NaOH, extracted with dichloromethane, evaporated to dryness, and chromatographed. After evaporating the good fraction, 2.37 g of the free base are obtained. This base is dissolved in 7.5 ml of absolute ethanol to which 1 ml of concentrated hydrochloric acid is added. The crystallised hydrochloride, after having been left to stand overnight at 0 °C, is sucked off, washed with little cold absolute ethanol and dried. Yield 2.0 g (53%). Melting-point 198-199 °C (decomposition).

c) 4H,8H-5,6,9,10,11,12-hexahydro-11-[(2-methyl)-1H--imidazol-1-yl)-methyl]-cyclohepta-[4,5]-pyrrolo--[3,2,1-ij]-quinolin-12-one

2.0 g (6 mmol) of 4H,8H-5,6,9,10,11,12-hexahydro-11-[(dimethylamino)-methyl]-cyclohepta-[4,5]-pyrrolo-[3,2,1-ij]-quinolin-12-one hydrochloride are mixed with 1.6 g (20 mmol) of 2-methylimidazole, 25 ml of water and 25 ml of n-propanal. The mixture is boiled under nitrogen for 48 hours while stirring. After cooling, the reaction mixture is poured out in 2N NaOH and extracted with dichloromethane,

evaporated and chromatographed. After evaporating the good fraction, 1.78 g (89%) of the desired compound are obtained. Melting-point 159-161 °C.

The compounds of formula 2 indicated in the following table have been prepared according to the method of Example I and II respectively.

TABLE

comp. no.	$(R_0)_n$	Z	m	R_2	R_3	R_4	salt	m.p. (°C)	method of example
1	H	$-CH_2CH_2-$	2	CH_3	H	H	base	226-227	I
2	H	$-CH_2-C(CH_3)-$	2	CH_3	H	H	base	190-191	I
3	H	$-CH_2-CH_2-CH_2-$	2	H	H	H	base	217-218	I
4	H	$-CH_2-CH_2-CH_2-$	2	C_2H_5	H	H	HCl	165-168	I
5	H	$-CH_2-CH_2-CH(CH_3)-$	2	CH_3	H	H	base	149-152	I
6	H	$-O-CH_2-CH_2-$	2	CH_3	H	H	base	230-231	I
7	H	$-S-CH_2-CH_2-$	2	CH_3	H	H	base	213-215	I
8	1-Cl	$-CH_2-CH_2-CH_2-$	2	CH_3	H	H	base	252-255	I
9	2-F	$-CH_2-CH_2-CH_2-$	2	CH_3	H	H	base	184-185.5	I
10	2-Cl	$-CH_2-CH_2-CH_2-$	2	CH_3	H	H	base	201-204	I
11	2-OCH_3	$-CH_2-CH_2-CH_2-$	2	CH_3	H	H	base	189.5-191.5	I
12	3-F	$-CH_2-CH_2-CH_2-$	2	CH_3	H	H	base	219-222	I
13	3-Cl	$-CH_2-CH_2-CH_2-$	2	CH_3	H	H	base	190.5-192.5	I
14	H	$-(CH_2)_4-$	2	CH_3	H	H	base	188.5-191	I
15	H	$-CH_2-CH_2$ 	2	CH_3	H	H	base	foam	I
16	H	$-(CH_2)_5-$	2	CH_3	H	H	HCl	231.2-231.6	I
17	H	$-CH_2-CH_2-CH_2$	3	CH_3	H	H	base	159-151	II
18	H	$-(CH_2)_4-$	3	CH_3	H	H	base	130-131	II
19	H	$-CH_2-CH_2$ 	3	CH_3	H	H	HCl	221.5-223.5	II
20	H	$-CH_2CH_2-CH_2-$	4	CH_3	H	H	base	180-182	II

EXAMPLE III

(-)-4,5,6,8,9,10-hexahydro-10-[(2-methyl-1H-imidazol-1-yl)methyl-11H-pyrido-[3,2,1-jk]-carbazol-11-one, hydrochloride

A solution of 12,5 g of (+)-di-p-toluyl-D-tartaric acid monohydrate in 125 ml of warm methanol was added to a solution of 9,8 g of (R, S)-4,5,6,8,9,10-hexahydro-10-[(2-methyl-1H-imidazol-1-yl)methyl]-11H-pyrido-[3,2,1-jk]-carbazol-11-one in 210 ml of warm methanol. The mixture was stirred overnight at room temperature. The suspension so obtained was then stirred for 1 hour at 0-5 °C. The solid substance was sucked off, washed with cold methanol, petroleum ether, and dried. Yield: 18.7 g.

The obtained salt was dissolved in 465 ml of dimethylformamide (DMF) while heating. An amount of 230 ml of warm water was added slowly, and the mixture was cooled to room temperature while stirring. After a night at room temperature the solid substance was sucked off, washed with cold DMF/water (2:1), with absolute ethanol, with ether, and dried. Yield 14.6 g.

This crystallisation procedure was repeated twice using 25 ml of the (2:1) mixture of DMF and water per 1 g of the above salt. Yield: 7.9 g having a melting point of 155-157 °C (decomposition), and $[\alpha]_D^{25}$ = +76° (c = 0.3; methanol).

A solution of 1.6 ml of acetyl chloride in 15 ml of absolute alcohol was added to a suspension of 7.8 g of the above obtained salt in 75 ml of absolute alcohol. The solution so obtained was evaporated almost to dryness under reduced pressure and at a temperature below 45 °C. The residue was stirred into ethyl acetate. The solid substance was sucked off and washed with ethyl acetate. The solid substance was then stirred into isopropanol, sucked off, washed with isopropanol and with petroleum ether, and dried. Yield 3.6 g. Melting point: 226-228 °C. $[\alpha]_D^{25}$ = -5.0° (c = 1.8; methanol).

EXAMPLE IV

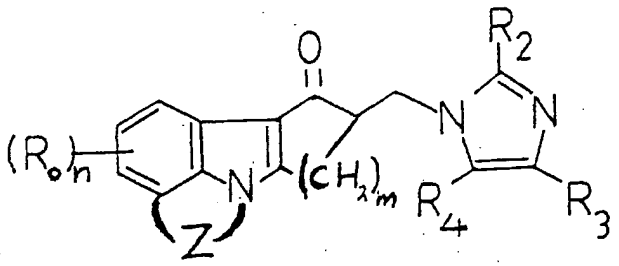
(+)-4,5,6,8,9,10-hexahydro-10-[(2-methyl-1H-imidazol-1-yl)methyl]-11H-pyrido-[3,2,1-jk]-carbazol-11-one, hydrochloride

In the same manner as described in Example III the isomer having the opposite rotation was obtained from 15.0 g of (R, S)-4,5,6,8,9,10-hexahydro-10-[(2-methyl-1H-imidazol-1-yl)methyl]-11H-pyrido-[3,2,1-jk]-carbazol-11-one, using 19.0 g of (-)-di-p-toluyl-L-tartaric acid monohydrate. Yield 4.15 g of the desired hydrochloride having a melting point of 223-225 °C (decomposition), and $[\alpha]_D^{25}$ = +4.4° (c = 1.7; methanol).

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Compounds of formula 2



(2)

wherein

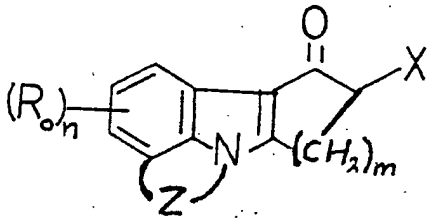
- R_0 is alkyl or alkoxy having 1-4 C-atoms, phenylalkoxy having 1-3 C-atoms in the alkoxy group, hydroxy, halogen, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, or a group $R_7S(O)_p$, wherein R_7 is alkyl having 1-4 C-atoms and p has the value 0, 1 or 2, or R_0 is a group R_8R_9N, R_8R_9N-CO-CH_2- or R_8R_9-N-CO wherein R_8 and R_9 are hydrogen or alkyl having 1-4 C-atoms or R_8R_9N forms a saturated 5- or 6-ring and n has the value 0, 1 or 2, Z together with the carbon atom and nitrogen atom to which Z is bound and the intermediate carbon atom, forms a heterocyclic group consisting of 5-8 ring atoms, in which, in addition to the nitrogen atom already present, a -CO-group or a second hetero atom from the group N, O, S, S-O or SO_2 may be present, which ring may be substituted with 1-3 alkyl groups having 1-4 C-atoms, a phenyl group or a spiroalkyl group (C_2-C_5) , or which ring may be anellated with a saturated or non-saturated carbocyclic or heterocyclic ring which consists of 5- or 6-ring atoms and which may be substituted with halogen, alkyl or alkoxy having 1-4 C-atoms, and m has the values 1-5,
- one of the groups R_2, R_3 and R_4 is hydrogen, alkyl having 1-6 C-atoms, cycloalkyl having 3-7 C-atoms, alkenyl having 2-6 C-atoms or phenylalkyl having 1-3 C-atoms in the alkyl group, and the two other groups independently of each other are hydrogen or alkyl having 1-6 C-atoms,

and the pharmaceutically acceptable acid addition salts thereof.

2. Pharmaceutical compositions which comprise at least one compound as claimed in Claim 1 as an active substance.

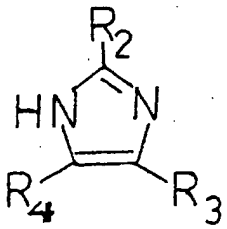
3. A method of preparing pharmaceutical compositions as claimed in Claim 2, characterized in that a compound as claimed in Claim 1 is brought into a form suitable for administration.

4. A method of preparing compounds as claimed in Claim 1, characterized in that a compound of formula 2 wherein the symbols have the meanings mentioned in Claim 1 is prepared by reacting a compound of formula 3



(3)

wherein R_0, n, Z and m have the meanings mentioned in Claim 1 and X is a reactive group, with a compound of formula 4



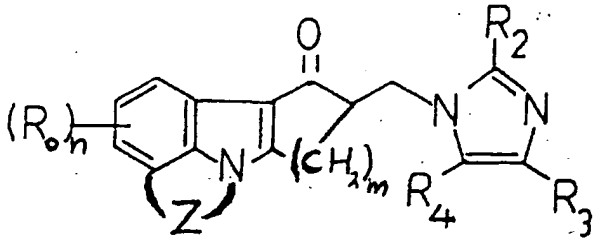
(4)

wherein R_2, R_3 and R_4 have the meanings mentioned in Claim 1.

5. A method as claimed in Claim 4, characterized in that a compound of formula 3 wherein X is the group $=CH_2$ or $-CH_2N(CH_3)_2$ is used as a starting material.

Claims for the following Contracting States : ES, GR

1. A method of preparing pharmaceutical compositions, characterized in that a compound having general formula 2



(2)

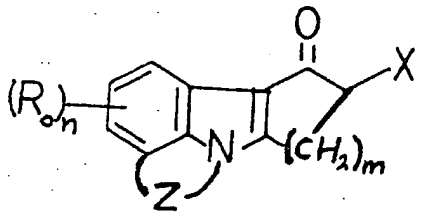
wherein

- R_0 is alkyl or alkoxy having 1-4 C-atoms, phenylalkoxy having 1-3 C-atoms in the alkoxy group, hydroxy, halogen, trifuoromethyl, trifuoromethoxy, trifluoromethylthio, or a group $R_7S(O)_p$, wherein

R_7 is alkyl having 1-4 C-atoms and p has the value 0, 1 or 2, or R_6 is a group R_8R_9N, R_8R_9N-CO-CH_2- or R_8R_9-N-CO wherein R_8 and R_9 are hydrogen or alkyl having 1-4 C-atoms or R_8R_9N forms a saturated 5- or 6-ring and n has the value 0, 1 or 2, Z together with the carbon atom and nitrogen atom to which Z is bound and the intermediate carbon atom, forms a heterocyclic group consisting of 5-8 atoms, in which, in addition to the nitrogen atom already present, a -CO-group or a second hetero atom from the group N, O, S, S-O or SO_2 may be present, which ring may be substituted with 1-3 alkyl groups having 1-4 C-atoms, a phenyl group or a spiroalkyl group (C_2-C_5), or which ring may be anellated with a saturated or non-saturated carbocyclic or heterocyclic ring which consists of 5- or 6-ring atoms and which may be substituted with halogen, alkyl or alkoxy having 1-4 C-atoms, and m has the values 1-5,

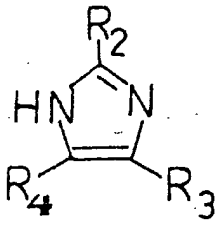
- one of the groups R_2, R_3 and R_4 is hydrogen, alkyl having 1-6 C-atoms, cycloalkyl having 3-7 C-atoms, alkenyl having 2-6 C-atoms or phenylalkyl having 1-3 C-atoms in the alkyl group, and the two other groups independently of each other are hydrogen or alkyl having 1-6 C-atoms, or a pharmaceutically acceptable acid addition salt thereof is brought into a form suitable for administration.

2. A method of preparing compounds as used in Claim 1, characterized in that a compound of formula 2 wherein the symbols have the meanings mentioned in Claim 1 is prepared by reacting a compound of formula 3



(3)

wherein R_6, n, Z and m have the meanings mentioned in Claim 1 and X is a reactive group, with a compound of formula 4



(4)

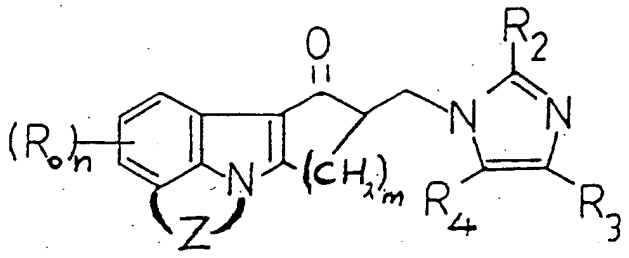
wherein R_2, R_3 and R_4 have the meanings mentioned in Claim 1.

3. A method as claimed in Claim 2, characterized in that a compound of formula 3 wherein X is the group $=CH_2$ or $-CH_2N(CH_3)_2$ is used as a starting material

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindungen der Formel (2)



(2),

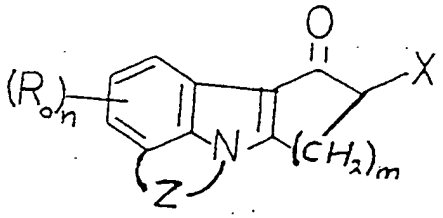
worin

- R_o Alkyl oder Alkoxy mit 1 bis 4 C-Atomen, Phenylalkoxy mit 1 bis 3 C-Atomen in der Alkoxygruppe, Hydroxy, Halogen, Trifluormethyl, Trifluormethoxy, Trifluormethylthio oder eine Gruppe $R_7S(O)_p$ darstellt, worin R_7 Alkyl mit 1 bis 4 C-Atomen bedeutet und p den Wert Null, 1 oder 2 aufweist, oder R_o eine Gruppe R_8R_9N, R_8R_9N-CO-CH_2- oder R_8R_9-N-CO ist, worin R_8 und R_9 Wasserstoff oder Alkyl mit 1 bis 4 C-Atomen bedeutet oder R_8R_9N einen gesättigten 5- oder 6-gliedrigen Ring bildet und n den Wert Null, 1 oder 2 aufweist, Z zusammen mit dem Kohlenstoffatom und dem Stickstoffatom, an welche Z gebunden ist, und dem dazwischenliegenden Kohlenstoffatom, eine aus 5 bis 8 Ringatomen bestehende heterocyclische Gruppe bildet, in welcher, zusätzlich zu dem bereits vorhandenen Stickstoffatom, eine -CO-Gruppe oder ein zweites Heteroatom aus der Gruppe N, O, S, S-O oder SO_2 vorhanden sein kann, welcher Ring durch 1 bis 3 Alkylgruppen mit 1 bis 4 C-Atomen, eine Phenylgruppe oder eine Spiroalkylgruppe (C_2-C_5) substituiert sein kann, oder welcher Ring an einen gesättigten oder ungesättigten, carbocyclischen oder heterocyclischen Ring anelliert sein kann, welcher aus 5 oder 6 Ringatomen besteht und welcher durch Halogen, Alkyl oder Alkoxy mit 1 bis 4 C-Atomen substituiert sein kann, und m die Werte 1 bis 5 aufweist,
- eine der Gruppen R_2, R_3 und R_4 Wasserstoff, Alkyl mit 1 bis 6 C-Atomen, Cycloalkyl mit 3 bis 7 C-Atomen, Alkenyl mit 2 bis 6 C-Atomen oder Phenylalkyl mit 1 bis 3 C-Atomen in der Alkylgruppe bedeutet und die beiden anderen Gruppen unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen darstellen, und die pharmazeutisch annehmbaren Säureadditionssalze hievon.

2. Pharmazeutische Zusammensetzungen, welche wenigstens eine Verbindung wie in Anspruch 1 beansprucht als aktive Substanz umfassen.

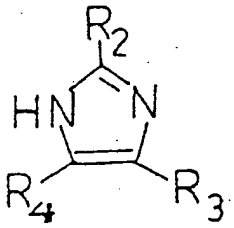
3. Verfahren zur Herstellung pharmazeutischer Zusammensetzungen nach Anspruch 2, dadurch gekennzeichnet, daß eine Verbindung wie in Anspruch 1 beansprucht in eine zur Verabreichung geeignete Form gebracht wird.

4. Verfahren zur Herstellung von Verbindungen wie in Anspruch 1 beansprucht, dadurch gekennzeichnet, daß eine Verbindung der Formel (2), worin die Symbole die in Anspruch 1 erwähnten Bedeutungen haben, durch Umsetzen einer Verbindung der Formel (3)



(3),

worin R_0, n, Z und m die in Anspruch 1 erwähnten Bedeutungen haben und X eine reaktive Gruppe ist, mit einer Verbindung der Formel (4)



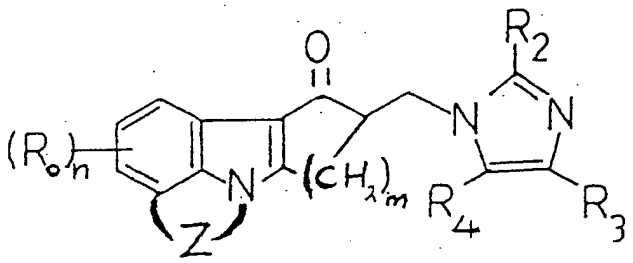
(4),

worin R_2, R_3 und R_4 die in Anspruch 1 erwähnten Bedeutungen haben, hergestellt wird.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß eine Verbindung der Formel (3), worin X die Gruppe $=CH_2$ oder $-CH_2N(CH_3)_2$ darstellt, als Ausgangsmaterial verwendet wird.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung pharmazeutischer Zusammensetzungen, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel (2)

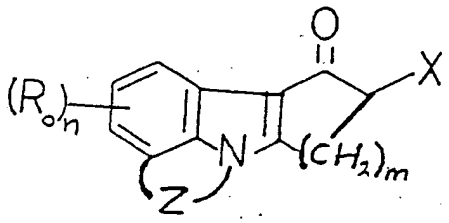


(2),

worin

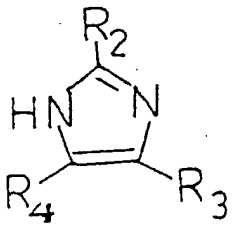
- R_0 Alkyl oder Alkoxy mit 1 bis 4 C-Atomen, Phenylalkoxy mit 1 bis 3 C-Atomen in der Alkoxygruppe, Hydroxy, Halogen, Trifluormethyl, Trifluormethoxy, Trifluormethylthio oder eine Gruppe $R_7S(O)_p$ darstellt, worin R_7 Alkyl mit 1 bis 4 C-Atomen bedeutet und p den Wert Null, 1 oder 2 aufweist, oder R_0 eine Gruppe R_8R_9N, R_8R_9N-CO-CH_2- oder R_8R_9-N-CO ist, worin R_8 und R_9 Wasserstoff oder Alkyl mit 1 bis 4 C-Atomen bedeutet oder R_8R_9N einen gesättigten 5- oder 6-gliedrigen Ring bildet und n den Wert Null, 1 oder 2 aufweist, Z zusammen mit dem Kohlenstoffatom und dem Stickstoffatom, an welche Z gebunden ist, und dem dazwischenliegenden Kohlenstoffatom, eine aus 5 bis 8 Atomen bestehende heterocyclische Gruppe bildet, in welcher, zusätzlich zu dem bereits vorhandenen Stickstoffatom, eine -CO-Gruppe oder ein zweites Heteroatom aus der Gruppe H, O, S, S-O oder SO_2 vorhanden sein kann, welcher Ring durch 1 bis 3 Alkylgruppen mit 1 bis 4 C-Atomen, eine Phenylgruppe oder eine Spiroalkylgruppe (C_2-C_5) substituiert sein kann, oder welcher Ring an einen gesättigten oder ungesättigten, carbocyclischen oder heterocyclischen Ring anelliert sein kann, welcher aus 5 oder 6 Ringatomen besteht und welcher durch Halogen, Alkyl oder Alkoxy mit 1 bis 4 C-Atomen substituiert sein kann, und m die Werte 1 bis 5 aufweist,
- eine der Gruppen R_2, R_3 und R_4 Wasserstoff, Alkyl mit 1 bis 6 C-Atomen, Cycloalkyl mit 3 bis 7 C-Atomen, Alkenyl mit 2 bis 6 C-Atomen oder Phenylalkyl mit 1 bis 3 C-Atomen in der Alkylgruppe bedeutet und die beiden anderen Gruppen unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 C-Atomen darstellen, oder ein pharmazeutisch annehmbares Säureadditionssalz hievon in eine zur Verabreichung geeignete Form gebracht wird.

2. Verfahren zur Herstellung von Verbindungen wie in Anspruch 1 verwendet, dadurch gekennzeichnet, daß eine Verbindung der Formel (2), worin die Symbole die in Anspruch 1 erwähnten Bedeutungen haben, durch Umsetzen einer Verbindung der Formel (3)



(3),

worin R_0, n, Z und m die in Anspruch 1 erwähnten Bedeutungen haben und X eine reaktive Gruppe ist, mit einer Verbindung der Formel (4)



(4),

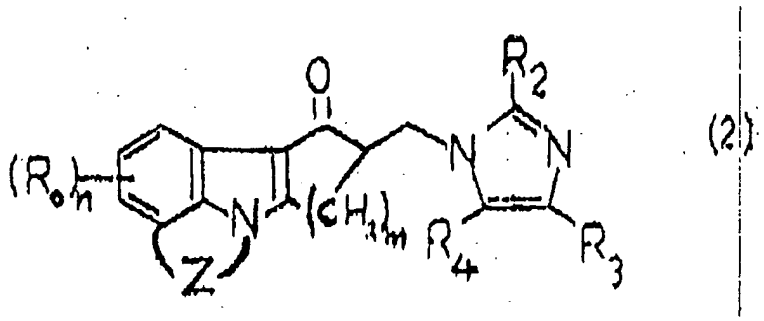
worin R_2, R_3 und R_4 die in Anspruch 1 erwähnten Bedeutungen haben, hergestellt wird.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß eine Verbindung der Formel (3), worin X die Gruppe $=CH_2$ oder $-CH_2N(CH_3)_2$ darstellt, als Ausgangsmaterial verwendet wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composés de formule 2



(2)

dans laquelle

- R_0 est un alkyle ou un alcoxy ayant de 1 à 4 atomes de carbone, un phénylalcoxy ayant de 1 à 3 atomes de carbone dans le groupe alcoxy, un hydroxy, un halogène, un trifluorométhyle, un trifluorométhoxy, un trifluorométhylthio, ou un groupe $R_7S(O)_p$, où R_7 est un alkyle ayant de 1 à 4: atomes de carbone et p à la valeur 0, 1 ou 2, ou R_0 est un groupe R_8R_9N, R_8R_9N-CO-CH_2- ou R_8R_9-N-CO- où R_8 et R_9 représentant un hydrogène ou un alkyle ayant de 1 à 4 atomes de carbone ou R_8R_9N forme un noyau à 5 ou 6 chaînons saturé et n a la valeur 0, 1 ou 2, 2 avec l'atome de carbone et l'atome d'azote auxquels il est lié et l'atome de carbone intermédiaire forme un groupe hétérocyclique constitué de 5 à 8 atomes dans le noyau dans lequel, outre

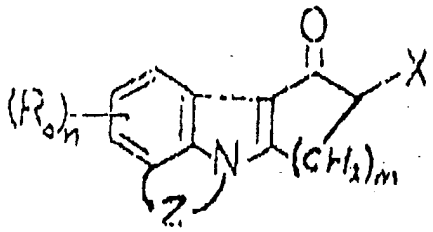
l'atome d'azote déjà présent, un groupe -CO- ou un second hétéroatome du groupe N, O, S, S-O ou SO_2 peut être présent, lequel noyau peut être substitué par de 1 à 3 groupes alkyle ayant de 1 à 4 atomes de carbone, un groupe phényle ou un groupe spiroalkyle (C_2-C_5), ou lequel noyau peut être condensé avec un noyau carbocyclique ou hétérocyclique saturé ou non saturé qui se compose de 5 ou 6 atomes dans le cycle et qui peut être substitué par un halogène, un alkyle ou un alcoxy ayant de 1 à 4 atomes de carbone, et m à les valeurs 1-5, l'un des groupes R_2 , R_3 et R_4 est un hydrogène, un alkyle ayant de 1 à 6 atomes de carbone, un cycloalkyle ayant de 3 à 7 atomes de carbone, un alcényle ayant de 2 à 6 atomes de carbone ou un phénylalkyle ayant de 1 à 3 atomes de carbone dans la groupe alkyle, et les deux autres groupes représentent indépendamment l'un de l'autre un hydrogène ou un alkyle ayant de 1 à 6 atomes de carbone,

et leurs sels d'addition d'acides pharmaceutiquement acceptables.

2. Compositions pharmaceutiques qui comprennent au moins un composé selon la revendication 1 comme substance active.

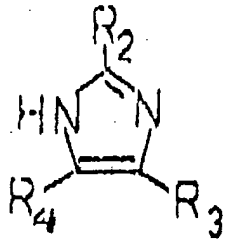
3. Procédé de préparation de compositions pharmaceutiques selon la revendication 2, caractérisé en ce qu'on met un composé selon la revendication 1 sous une forme appropriée à l'administration.

4. Procédé de préparation de composés selon la revendication 1, caractérisé en ce qu'on prépare un composé de formule 2 dans laquelle les symboles ont les significations mentionées dans la revendication 1 en faisant réagir un composé de formule 3



(3)

dans laquelle R_0 , n , Z et m ont les significations mentionnées dans la revendication 1 et X est un groupe réactif, avec un composé de formule 4



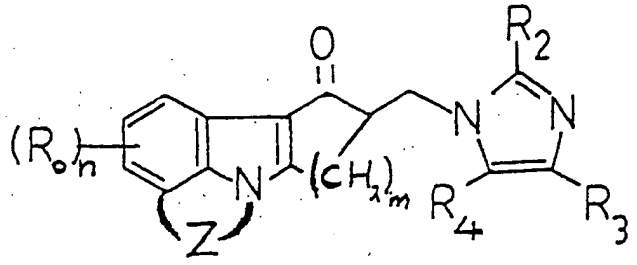
(4)

dans laquelle R_2 , R_3 et R_4 ont les significations mentionnées dans la revendication 1.

5. Procédé selon la revendication 4, caractérisé en ce qu'on utilise comme produit de départ un composé de formule 3 dans laquelle X est le groupe $=CH_2$ ou $-CH_2N(CH_3)_2$.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation de compositions pharmaceutiques, caractérisé en ce qu'on met sous une forme appropriée à l'administration un composé de formule générale (2)

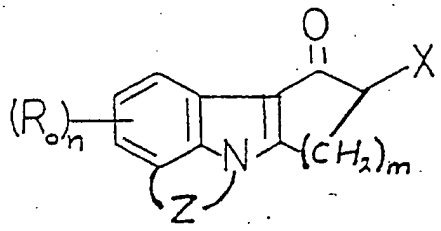


(2)

dans laquelle

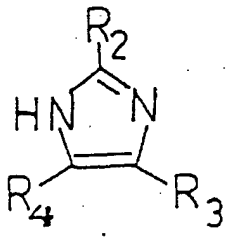
- R_o représente un groupe alkyle ou alcoxy ayant 1 à 4 atomes de carbone, phénylalcoxy ayant 1 à 3 atomes de carbone dans le groupe alcoxy, hydroxyle, halogéno, trifluorométhyle, trifluorométhoxy, trifluorométhylthio, ou un groupe $R_7S(O)_p$, formule dans laquelle R_7 représente un groupe alkyle ayant 1 à 4 atomes de carbone et p vaut 0, 1, ou 2, ou bien R_o est un groupe R_8R_9N, R_8R_9,N-CO-CH_2- et/ou R_8R_9,N-CO, où R_8, R_9 représentent chacun un atome d'hydrogène ou un groupe alkyle ayant 1 à 4 atomes de carbone, ou bien R_8R_9N forme un noyau saturé comportant 5 ou 6 chaînons et n vaut 0, 1 ou 2; Z forme, avec l'atome de carbone et l'atome d'azote auxquels Z est lié et avec l'atome de carbone intermédiaire un groupe hétérocyclique consistant en 5 à 8 atomes dans lequel, en plus de l'atome d'azote déjà présent, il peut y avoir présence d'un groupe -CO- ou d'un second hétéro atome pris parmi l'ensemble N, O, S, S-O ou SO_2, lequel noyau peut être substitué par 1 à 3 groupes alkyles ayant 1 à 4 atomes de C, par un groupe phényle ou par un groupe spiroalkyle (C_2-C_5), ou bien lequel noyau peut être condensé avec un noyau carbocyclique ou hétérocyclique, saturé ou non saturé, qui se compose de 5 ou 6 atomes dans le cycle et qui peut être substitué par de l'halogène, par un groupe alkyle ou alcoxy ayant 1 à 4 atomes de C et m vaut 1 à 5,
  l'un des groupes R_2, R_3, et R_4 est un atome d'hydrogène, un groupe alkyle ayant 1 à 6 atomes de C, cycloalkyle ayant 3 à 7 atomes de C, alcényle ayant 2 à 6 atomes de C, ou phényl alkyle ayant 1 à 3 atomes de C dans le groupe alkyle, et les deux autres groupes représentent chacun, indépendamment l'un de l'autre, un atome d'hydrogène ou un groupe alkyle ayant 1 à 6 atomes de C, ou un sel d'addition avec un acide, pharmaceutiquement acceptable, de ce composé.

2. Procédé de préparation de composés tels qu'utilisés dans la revendication 1, caractérisé en ce qu'on prépare un composé de formule 2, dans laquelle les symboles ont les sens mentionnés à la revendication 1, en faisant réagir un composé de formule 3 :



(3)

(dans laquelle R_o, n , Z et m ont les sens mentionnés à la revendication 1 et X représente un groupe réactif) avec un composé de formule 4



(4)

dans laquelle R_2, R_3, R_4 ont les sens mentionnés à la revendication 1.

3. Procédé tel que revendiqué à la revendication 2, caractérisé en ce qu'on utilise comme matière de départ un composé de formule 3, dans laquelle X représente le groupe = CH_2 ou $-CH_2N(CH_3)_2$.